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SPIEGEL, S

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), No days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☒ Information on How to Effect Drawing Changes, PTO-1474.
6. ☒ Listing of Bonded Draftsmen.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-18 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-18 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

INFORMALITIES

The drawings are objected to for reasons on the accompanying NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW (PTO-948). Correction is required.

The disclosure is objected to because of the following informalities: on page 3, lines 10 and 27; on page 7, line 29; and on page 10, line 12, "Cobas-fara" should be -- Cobas-FARA --. Appropriate correction is required.

NON-ART BASED REJECTIONS

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention.

The axes and/or peaks on Figure 2 are not labelled. Applicant is cautioned against introducing new matter when making changes involving the drawings. Proposed drawing correction and/or the proposed substitute sheets of drawings must be embodied in a separate letter and show such changes in red ink.

Claims 1-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-18 fail to recite clear, distinct and positive method steps. Claims 1 and 11 appear to be substantial duplicates because claims 1, which inherently requires a method step of collecting a serum sample, and 11 recite identical method steps. Claims 1, 11 and 12 are inconsistent in reciting "detecting the presence of hemolyzed erythrocytes in blood", "diagnosing a hemolytic condition", and "monitoring the level of hemolysis in a subject being treated for hemolysis" in their respective preambles but failing to

recite a positive method step of actually detecting hemolyzed erythrocytes, diagnosing a hemolytic condition, or monitoring the efficacy of an anti-hemolysis treatment and in failing to recite a positive method step correlating the detected erythrocyte adenylate kinase activity to such. It is unclear if the mere presence of any detectable erythrocyte adenylate kinase activity in serum is correlative of hemolyzed erythrocytes, diagnostic of a hemolytic condition, etc. or whether some sort of cut-off value is required.

Claims 2-3 and 14-15 imply, rather than positively state, a particular reagent system is required to provide a specific reaction product which can be measured by the explicitly required detection means, such as ultraviolet light (e.g. a fluorescent product, such as NAD(H)?) and absorbance (e.g. a chromogen?). Critical limitations should be positively stated, not merely implied.

Claim 2, line 2 is confusing in reciting "if present". The phrase appears inherent in claim 1 and, therefore, superfluous. It is suggested that "if any" be deleted from claim 2, line 2.

In claim 4, line 4, insert --said-- before "erythrocyte" for proper antecedent basis.

Claims 5-9 fail to recite clear, distinct and positive method steps; and, are unclear in reciting "effected by".

Analogous criticisms apply to claims 11-18.

It is suggested that claim 11 recite --hemolysis-- instead of "a hemolytic condition" since no specific condition(s) are being referred, simply the manifestation "hemolysis".

Claims 1-18 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 requires detecting erythrocyte adenylate kinase ACTIVITY, i.e. a FUNCTIONAL determination, while claims 16-18 recite detecting antibody binding, i.e. a MASS determination. The specification suggests that the mere presence of erythrocyte adenylate kinase is intended to be detected, irregardless of whether the erythrocyte adenylate kinase is measured functionally or by mass action. Therefore, it is suggested that "activity" be deleted from claim 12, line 4.

Claims 2, 14 and 15 are vague and indefinite in reciting "an adenylate kinase-specific visualization reagent." Since adenylate kinase, like lactate dehydrogenase, is a family of isoenzymes coming from a number of different sources in addition to erythrocytes, such as liver, muscle, etc. it is unclear whether "an adenylate kinase-specific visualization reagent" refers to a reagent specifically reactive with only the erythrocyte adenylate kinase isoenzyme or with any and all adenylate kinases irregardless of tissue origin. The specification explicitly suggests that determination of total serum enzyme level in the case of an enzyme coming from multiple tissue sources is to be avoided as an "indirect" indication. The specification teaches that the adenylate kinase isoenzymes in the serum must be separated by some differential means so that the erythrocyte isoenzyme can be specifically measured, such as by an electrophoretic separation or by an immunochemical separation using specific antibodies. Furthermore, in view of the teaching in the specification that other kinase isoenzymes co-migrate and co-react with kinase substrates, the specification is only enabled for a visualization reagent/reaction as set forth in the paragraph bridging pages 4-5 (see Massey et al. *infra*). It would require undue experimentation to ascertain alternative functional assays to not only separate adenylate kinase into its various isoenzymes so as to selectively measure the erythrocyte isoenzyme, but also to differentially measure adenylate kinase to the exclusion of other related, comigrating kinases, such as creatine kinase.

Claims 8-9 are confusing in reciting "isotopic means" and "nonisotopic means". The specification suggests these means refer to the type of label used on a tracer antibody which specifically binds to the erythrocyte adenylate kinase. However, the claims may be broadly read as intending a specific type of instrumentation, rather than reagent.

Claim 11 is vague and indefinite in reciting "diagnosing a hemolytic condition in a subject suspected of having a hemolytic condition". It is unclear whether a screening test, a confirmatory test or a definitive diagnosis is intended. The specification suggests the first alternative only. The specification fails to provide criteria defining a category of patients "suspected of having a hemolytic condition". Secondly, the prior art recognizes that a patient can have a hemolytic condition and a DEFICIENCY of erythrocyte adenylate kinase (see Beutler et al. and Matsuura et al. *infra*).

ART BASED REJECTIONS

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Mainzer et al. (Chemical Abstract 78(13):82705, 1973) and Henry (CLINICAL DIAGNOSIS and MANAGEMENT by Laboratory Methods, 16th ed. 1979, pp. 985-1032) in view of Le Gall et al. (Biological Abstract 62035415, 1975), Buth et al. (Biological Abstract 71059076, 1981), Kurokawa et al. (Biological Abstract 91006139, 1991) and Koyama et al. (*Mol. Immunol.* 20(8):851-856, 1983).

The claimed invention is directed to detection of hemolysis and/or conditions producing hemolysis by measuring serum adenylate kinase.

Mainzer et al. describe serum myokinase-(adenylate kinase) activity in intravascular hemolysis. Mainzer et al. found that on the whole free hemoglobin and adenylate kinase activity curves ran parallel when human erthyrocyte suspensions were hemolyzed with saline. Drug-induced hemolysis of rabbit erythrocytes shown a sharp increase in adenylate kinase activity. Two patients with severe intravascular hemolysis also showed sharp increases in adenylate kinase activity. Thus, Mainzer et al. teach a specific correlation between serum adenylate kinase and hemolysis.

Henry provides a generic discussion of the causes, manifestations, diagnostic testing, and clinical significance of a variety of hemolytic conditions and hemolysis in general.

Le Gall et al. determine adenylate kinase using cellulose acetate electrophoresis.

Buth et al. use NAD-dependent glucose-6-phosphate dehydrogenase in adenylate kinase enzyme staining/detecting procedures because it significantly less expensive than utilizing NADP.

Kurokawa et al. determine adenylate kinase isoform AK1 using Western blotting with an isoform-specific monoclonal antibody.

Koyama et al. describe a quantitative immunoprecipitation reaction for determining adenylate kinase.

Therefore, it would have been obvious to test for or detect hemolysis by measuring serum myokinase (adenylate kinase) activity from hemolyzed erythrocytes in view of its known correlation to hemolysis as taught and suggested by Mainzer et al. and in view of the known clinical significance of hemolysis and hemolytic conditions as taught by Henry. It would have been further obvious and well within ordinary skill in the art to measure erythrocyte adenylate kinase by any known and conventional assay, including electrophoretic separation and staining, such as with an NAD-dependent glucose-6-phosphate dehydrogenase visualization technique; immunoassay; immunoprecipitin assay; and Western blot analysis as suggested by Le Gall et al., Buth et al., Kurokawa et al. and/or Koyama et al.

CONCLUDING REMARKS

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Malaya et al. (Chemical Abstract 98(15):122060) state the accuracy of determining adenylate kinase activity in serum is increased by hemolyzing two blood samples to different degrees; separating the serum; determining the levels of hemoglobin and reduced pyridine dinucleotide in the serum; and calculating adenylate kinase activity from a formula.

MacGregor et al. (Chemical Abstract 78(17):107073) show a time sequence for release of intracellular molecules during gradual osmotic hemolysis -- K, hemoglobin monomer, adenylate kinase/hemoglobin dimer, and finally hemoglobin tetramer -- correlative to increasing molecular weight of these molecules.

Oepen et al. (Chemical Abstract 74(11):50386, 1971) uses thin layer starch gel electrophoresis to determine adenylate kinase types with blood stains.

Beutler et al. (*J. Clin. Invest.* 72(2):648-55, 1983) discusses a child with hemolytic anemia who was found to have severe erythrocyte adenylate kinase deficiency.

Matsuura et al. (*J. of Biol. Chem.* 264(17):10148-55, 1989) discuss erythrocyte adenylate kinase deficiency in hemolytic anemia.

Lee (US 5,330,420) provides a continuous, real-time hemolysis detector. The prior art determined whether hemolysis occurred by taking blood samples and subjecting them to analysis for artifacts of hemolysis, such as hemoglobin (col. 1, lines 20-27). The described apparatus is used with patients undergoing hemodialysis, hemoperfusion, blood transfusion or other extracorporeal blood therapies. During treatment, an initial optical measurement is made and if any hemolysis develops, hemoglobin appears in the plasma and changes the light transmission or reflectance in a light path chamber (col. 3, lines 1-6; col. 4, lines 51-55).

Yazawa et al. (US 4,877,579) describes a multilayer device for detecting bilirubin. Bilirubin is the metabolic product of hemoglobin. Determination of the amount of bilirubin in body fluid is important for the detection of hemolysis (col. 1, lines 19-22).

Massey et al. (*Clin. Chem.* 28(5):1174-1176, 1982) describe adenylate kinase "artifacts" in creatine kinase isoenzyme electrophoresis on cellulose acetate.

Oechsner et al. (*FEBS Lett.* 242(1):187-193, 1988) determine yeast mitochondrial adenylate kinase by Western blot analysis with specific antibody.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carol A. Spiegel whose telephone number is (703) 308-3986.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Carol A. Spiegel
June 29, 1995

Carol A. Spiegel

CAROL A. SPIEGEL
PRIMARY EXAMINER
GROUP 1800